When to Initiate Therapy in Antiretroviral-Naive Children (Updated August 11, 2011)

The decision on when to initiate antiretroviral therapy (ART) in asymptomatic HIV-infected older children, adolescents, and adults continues to generate controversy among HIV experts. Aggressive therapy in the early stages of HIV infection controls viral replication before the onset of rapid genetic mutation and evolution into multiple quasispecies, resulting in a lower viral set point, fewer mutant viral strains, and potentially less drug resistance[1]. Early therapy also slows immune system destruction and preserves immune function, preventing clinical disease progression. Additionally, ongoing viral replication may be associated with persistent inflammation and development of cardiovascular, kidney, and liver disease and malignancy; studies in adults suggest that early control of replication may reduce the occurrence of these non-AIDS complications[2-8]. Conversely, delaying therapy until later in the course of HIV infection, when clinical or immunologic symptoms appear, may result in reduced evolution of drug-resistant virus because of a lack of drug selection pressure, improved adherence to the therapeutic regimen because the patient is symptomatic, and reduced or delayed adverse effects of ART. Because therapy in children is initiated at a young age and will likely be lifelong, concerns about toxicities are particularly important.

Randomized clinical trials have demonstrated the benefit in reducing mortality and morbidity with initiation of therapy in infants <12 weeks of age with normal CD4 percentage[9] and in adults with CD4 cell counts <350 cells/mm^3 [10]. However, clinical trial data on the optimal time to start treatment in older children or in adults with higher CD4 cell counts are lacking.

Based on observational cohort data demonstrating benefit of treatment in adults with CD4 cell counts between 350 and 500 cells/mm^3 in reducing morbidity and mortality, adult treatment guidelines recommend initiation of lifelong ART for individuals with CD4 cell counts ≤500 cells/mm^3 [11–14]. For adults with CD4 counts >500 cell/mm^3, observational data are inconclusive regarding the potential survival benefit of early treatment. Adult treatment guidelines note that some experts would recommend initiation of therapy at this CD4 level, while other experts would view initiation at this level as optional[13].

Recommendations on when to initiate therapy have generally been more aggressive in young children than in adults. HIV infection in children is primarily perinatally acquired, which makes it possible to identify the time of infection. HIV disease progression is more rapid in young children than in adults; and laboratory parameters are less predictive of risk of disease progression in children, particularly for infants younger than 1–2 years of age. As discussed in Laboratory Monitoring of Pediatric HIV Infection, CD4 counts and HIV RNA values vary considerably by age in children, and both markers are poorly predictive of disease progression and mortality in children <12 months of age[15]. Hence, recommendations for when to start therapy differ by age of the child. Based on data showing that surrogate marker-based risk of disease progression to AIDS or death varies considerably by age but that CD4 count-associated risk of progression in children ≥5 years of age is similar to risk in young adults[16], the Panel has moved to recommendations for initiation of treatment for three age bands: infants <12 months of age, children 1 to <5 years of age, and children and adolescents ≥5 years of age.

Antiretroviral-Naive HIV-Infected Infants 12 Months or Younger

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Panel's Recommendations (Table 7)

- Antiretroviral therapy (ART) should be initiated in HIV-infected infants <12 months of age, regardless of clinical status, CD4 percentage, or viral load **(AII)**.

- Issues associated with adherence must be fully assessed and discussed with the HIV-infected infant's caregivers before therapy is initiated **(AIII)**.

Data from the South African CHER Trial (Children with HIV Early Antiretroviral Therapy) demonstrated that initiating triple-drug ART before 12 weeks of age in asymptomatic perinatally infected children with normal CD4 percentage (CD4 percentage >25%), compared with delaying treatment until the child met clinical or immune criteria, resulted in a 75% reduction in early mortality[9]. Most of the deaths in the children in the delayed treatment arm occurred in the first 6 months after study entry. Because the risk of rapid progression is so high in young infants and based on the data from the CHER study, the Panel recommends initiation of therapy for all infants age <12 months regardless of clinical status, CD4 percentage, or viral load (Table 7). Before therapy is initiated, it is important to fully assess, discuss, and address issues associated with adherence with the HIV-infected infant's caregivers. However, given the high risk of disease progression and mortality in young HIV-infected infants, it is important to expedite this assessment in infants <12 months of age.

The risk of disease progression is inversely correlated with the age of the child, with the youngest children at greatest risk of rapid disease progression. Progression to moderate or severe immune suppression is also frequent in infected infants; by 12 months of age, approximately 50% of children develop moderate immune suppression and 20% develop severe immune suppression[17]. In the HIV Paediatric Prognostic Markers Collaborative Study meta-analysis, the 1-year risk of AIDS or death was substantially higher in younger children than in older children at any given level of CD4 percentage, particularly for infants <12 months of age[18]. Unfortunately, although the risk of progression is greatest in the first year of life, the ability to differentiate children at risk of rapid versus slower disease progression by clinical and laboratory parameters is also most limited in young infants. No specific "at-risk" viral or immunologic threshold can be easily identified, and progression of HIV disease and opportunistic infections (OIs) can occur in young infants with normal CD4 counts[18].

Identification of HIV infection during the first few months of life permits clinicians to initiate ART during the initial phases of primary infection. Data from a number of observational studies in the United States and Europe suggest that infants who receive early treatment are less likely to progress to AIDS or death than those who start therapy later[6,19-21]. Several small studies have demonstrated that despite the very high levels of viral replication in perinatally infected infants, early initiation of treatment can result in durable viral suppression and normalization of immunologic responses to non-HIV antigens in some infants. In infants with sustained control of plasma viremia, failure to detect extra-chromosomal replication intermediates suggests near-complete control of viral replication. Some of these infants have become HIV seronegative. However, therapy is not curative; proviral HIV-1 DNA continues to be detectable in peripheral blood lymphocytes and viral replication resumes if therapy is discontinued[22-23].

However, virologic suppression may take longer in young children (given their higher viral load at initiation of therapy) than in older children or adults[24-25]. Possible reasons for the poor response in infants include very high viral loads in young infants, inadequate antiretroviral (ARV) drug levels, and poor

adherence due to the difficulties in administering complex regimens to infants. With currently available drug regimens, rates of viral suppression of 70%–80% have been reported in HIV-infected infants initiating therapy at <12 months of age[6,26-27]. In a 5-year follow-up study of 40 HIV-infected children who

Table 7. Indications for Initiation of Antiretroviral Therapy in HIV-Infected Children

Table 7 provides general guidance rather than absolute recommendations for an individual patient. Factors to be considered in decisions about initiation of therapy include the risk of disease progression as determined by CD4 percentage or count and plasma HIV RNA copy number, the potential benefits and risks of therapy, and the ability of the caregiver to adhere to administration of the therapeutic regimen. Before making the decision to initiate therapy, the provider should fully assess, discuss, and address issues associated with adherence with the child (if age appropriate) and the caregiver.

Age Bands	Criteria for Therapy Initiation	Recommendations
<12 months	• Regardless of clinical symptoms, immune status, or viral load	*Treat (AII)*
1 to <5 years	• AIDS or significant HIV-related symptoms[a]	*Treat (AI*)*
	• CD4 percentage <25%, regardless of symptoms or HIV RNA level	*Treat (AII)*
	• Asymptomatic or mild symptoms[b] *and*	*Treat (BII)*
	o CD4 percentage ≥25% *and*	
	o HIV RNA ≥100,000 copies/mL	
	• Asymptomatic or mild symptoms[b] *and*	*Consider Treatment[c] (CIII)*
	o CD4 percentage ≥25% and	
	o HIV RNA <100,000 copies/mL	
≥5 years	• AIDS or significant HIV-related symptoms[a]	*Treat (AI*)*
	• CD4 count ≤500 cells/mm^3	*Treat* *CD4 count <350 cells/mm^3 (AI*)* *CD4 count 350–500 cells/mm^3 (BII*)*
	• Asymptomatic or mild symptoms[b] *and*	*Treat (BII*)*
	o CD4 count >500 cells/mm^3 *and*	
	o HIV RNA ≥100,000 copies/mL	
	• Asymptomatic or mild symptoms[b] *and*	*Consider Treatment[c] (CIII)*
	o CD4 count >500 cells/mm^3 *and*	
	o HIV RNA <100,000 copies/mL	

[a] CDC Clinical Categories C and B (except for the following Category B condition: single episode of serious bacterial infection)

[b] CDC Clinical Category A or N or the following Category B condition: single episode of serious bacterial infection

[c] Clinical and laboratory data should be re-evaluated every 3 to 4 months.

initiated treatment at <6 months of age, 98% had CD4 percentage >25% and 78% had undetectable viral load with median follow-up of 5.96 years[6].

Information on appropriate drug dosing in infants younger than 3–6 months is limited. Hepatic and renal functions are immature in the newborn undergoing rapid maturational changes during the first few months of life, which can result in substantial differences in ARV dose requirements between young infants and older children. When drug concentrations are subtherapeutic, either because of inadequate dosing, poor absorption, or incomplete adherence, ARV drug resistance can develop rapidly, particularly in the setting of high levels of viral replication in young infants. Frequent follow-up and continued assessment and support of adherence are especially important in the treatment of young infants (see Adherence to Antiretroviral Therapy in HIV-Infected Children and Adolescents).

Finally, the possibility of toxicities—such as lipodystrophy, dyslipidemia, glucose intolerance, osteopenia, and mitochondrial dysfunction—with prolonged therapy is a concern[28]. Whether it might be possible to stop therapy begun in early infancy after a defined period of treatment (e.g., 1–2 years) that protected the child during the period of greatest risk of HIV disease progression and mortality, and then restart therapy when the child meets standard age-related criteria, is under assessment in a clinical trial in South Africa.

Antiretroviral-Naive HIV-Infected Children 1 Year or Older

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• Antiretroviral therapy (ART) should be initiated in children age ≥1 year with AIDS or significant symptoms (Clinical Category C or most Clinical Category B conditions), regardless of CD4 percentage/count or plasma HIV RNA level (**AI***).

• Initiation of ART is also recommended for children age ≥1 year regardless of symptoms or plasma HIV RNA level if:

    • age 1 to <5 years and CD4 percentage <25% (**AII**); or

    • age ≥5 years and CD4 count ≤500 cells/mm^3 (**AI*** for CD4 percentage <25% or CD4 count <350 cells/mm^3 and **BII*** for CD4 count 350–500 cells/mm^3).

• Initiation of ART is also recommended for children age ≥1 year who are asymptomatic or have mild symptoms (Clinical Categories N and A or a single episode of serious bacterial infection) with a plasma RNA ≥100,000 copies/mL regardless of CD4 percentage/count (**BII***).

• Initiation of ART may be considered for children age ≥1 year who are asymptomatic or have mild symptoms with a plasma RNA RNA <100,000 copies/mL and CD4 percentage >25% if age 1–5 years or CD4 count >500 cells/mm^3 if age ≥5 years (**CIII**).

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Disease progression is less rapid in children age ≥1 year[17]. Children with clinical AIDS or significant symptoms (Clinical Category C or B—Table 6)[29] are at high risk of disease progression and death. The Panel recommends treatment for all such children, regardless of immunologic or virologic status. However, children age ≥1 year who have mild clinical symptoms (Clinical Category A) or who are asymptomatic (Clinical Category N) are at lower risk of disease progression than children with more severe clinical symptoms[30]. It should also be noted that some Clinical Category B conditions, such as a single episode of serious bacterial infection, may be less prognostic of the risk of disease progression. Consideration of CD4 count and viral load may be useful in determining the need for therapy in children with these conditions.

In adults, considerations related to initiation of ART in asymptomatic individuals are based primarily on risk of disease progression as determined by baseline CD4 count[13]. In adults, both clinical trial and observational data support initiation of treatment in individuals with CD4 counts <350 cells/mm³. In HIV-infected adults in Haiti, a randomized clinical trial found significant reductions in mortality and morbidity with initiation of treatment when CD4 counts fell to <350 cells/mm³ compared with deferring treatment until CD4 counts fell to <200 cells/mm³ [9]. In observational data in adults, a collaborative analysis of data from 12 adult cohorts in North America and Europe on 20,379 adults starting treatment between 1995 and 2003 showed the risk of AIDS or death was significantly less in adults who started treatment with CD4 counts of 200–350 cells/mm³ compared with those who started therapy at CD4 counts of <200 cells/mm³ [31].

No randomized trial data exist to address the comparative efficacy of starting versus deferring treatment at higher CD4 thresholds in HIV-infected adults or children. Two observational studies in adults, the ART Cohort Collaboration (ART-CC) and NA-Accord, suggest a higher rate of progression to AIDS or death in patients deferring treatment until CD4 count is <350 cells/mm³ compared with patients starting ART at CD4 counts of 351–500 cells/mm³ [11–12]. The NA-Accord study demonstrated a benefit of starting treatment at CD4 counts >500 cells/mm³ compared with starting ART at CD4 counts below this threshold[11]; however the ART-CC cohort found no additional benefit for patients starting ART with CD4 counts >450 cells/mm³ [11]. There are no similar observational data analyses for HIV-infected children. The Health and Human Services (HHS) Adult Antiretroviral Guidelines Panel recommends initiation of therapy for adults with CD4 cell counts ≤500 cells/mm³. The Adult Panel, however, was divided on recommendations regarding starting therapy in HIV-infected adults with CD4 counts >500 cells/mm³. Some experts recommend initiation of treatment while others feel that, at this level, therapy should be optional and considered on a case-by-case basis[32].

In children, the prognostic significance of a specific CD4 percentage or count varies with age[15,18]. In data from the HIV Paediatric Prognostic Markers Collaborative Study meta-analysis, derived from 3,941 children with 7,297 child-years of follow-up, the risk of mortality or progression to AIDS per 100 child-years is significantly higher for any given CD4 count among children age 1–4 years than among children age ≥5 years (Tables 3–4 and Figures 1–2). Data from the HIV Paediatric Prognostic Markers Collaborative Study suggest that absolute CD4 cell count is a useful prognostic marker for disease progression in children age ≥5 years, with risk of progression similar to that observed in adults (Table 4) [16,18]. For children age 1 to <5 years, a similar increase in risk of AIDS or death is seen when CD4 percentage drops below 25% (Table 3).

The level of plasma HIV RNA may provide useful information in terms of risk of progression, although its prognostic significance is weaker than CD4 count[15]. Several studies have shown that older children with HIV RNA levels ≥100,000 copies/mL are at high risk of mortality[33-35]; similar findings have been reported in adults[36]. Similarly, in the HIV Paediatric Prognostic Markers Collaborative Study meta-analysis, the 1-year risk of progression to AIDS or death rose sharply for children age >1 year when HIV RNA levels were ≥100,000 copies/mL (Table 3 and Figures 4–5)[15]. For example, the estimated 1-year risk of death was 2−3 times higher in children with plasma HIV RNA of 100,000 copies/mL compared with 10,000 copies/mL and 8−10 times higher with plasma HIV RNA >1,000,000 copies/mL.

Similar to data in adults, data from pediatric studies suggest the immune response to treatment in children is better when treatment is initiated at higher CD4 percentage/count levels[25,37]. In a study of 1,236 perinatally infected children in the United States, only 36% of those who started treatment with CD4 percentage <15% and 59% of those starting with CD4 percentage 15%–24% achieved CD4 percentage >25% after 5

years of therapy[38]. Younger age at initiation of therapy has also been associated with improved immune response and with more rapid growth reconstitution[37-39]. Given that disease progression in children age ≥5 years is similar to that in adults[15], and observational data in adults show decreased risk of mortality with initiation of therapy when CD4 cell count is ≤500 cells/mm³ [11-12], some experts feel that recommendations for asymptomatic children in this age range should be similar to those for adults. However, there are no pediatric data to address the optimal CD4 cell count threshold for initiation of therapy in older children; research studies are needed to answer this question in children more definitively.

Drug choices are more limited in children than in adults and adequate data to address the potential long-term toxicities of prolonged ART in a developing child are not yet available. Some studies have shown that a small proportion of perinatally infected children may be long-term nonprogressors, with no immunologic or clinical progression by 10 years of age despite no ART[40-42].

Based on the accumulated data, the Panel provides the following recommendations for treatment of children age 1 to <5 years. ART should be initiated in children age 1 to <5 years who have AIDS or significant HIV-related symptoms (CDC Clinical Categories C and B, except for the following Category B condition: single episode of serious bacterial infection [Table 6]), regardless of CD4 percentage/count or HIV RNA level. Additionally, treatment is recommended for children in this age group if they have a CD4 percentage <25%, regardless of clinical symptoms or HIV RNA level. Treatment is also recommended for children who are asymptomatic or have mild symptoms (Clinical Categories N and A, or Clinical Category B disease due to a single episode of serious bacterial infection [Table 6]) with CD4 percentage ≥25% if plasma HIV RNA is >100,000 copies/mL. ART may be considered for asymptomatic children age 1 to <5 years who have CD4 percentages ≥25% and who also have plasma HIV RNA levels <100,000 copies/mL.

For children age ≥5 years, ART should be initiated if they have AIDS or significant HIV-related symptoms (CDC Clinical Categories C and B, except for the following Category B condition: single episode of serious bacterial infection [Table 6]), regardless of CD4 percentage/count or HIV RNA level. Additionally, treatment is recommended for children in this age group if they have CD4 counts ≤500 cells/mm³, regardless of clinical symptoms or HIV RNA level. The evidence for this recommendation is strongest for children with CD4 counts <350 cells/mm³. For children with CD4 counts 350–500 cells/mm³, the recommendation is based on observational data in adults and hence the evidence base is not as strong; this recommendation should not prohibit research studies in children designed to answer this question more definitively. Treatment is also recommended for children who are asymptomatic or have mild symptoms (Clinical Categories N and A, or Clinical Category B disease due to a single episode of serious bacterial infection [Table 6]) with CD4 counts >500 cells/mm³ if HIV RNA is >100,000 copies/mL. ART may be considered for asymptomatic or mildly symptomatic children age ≥5 years who have CD4 counts >500 cells/mm³ and who also have plasma HIV RNA levels <100,000 copies/mL.

In general, except in infants and children with advanced HIV infection, ART does not need to be started immediately. Before initiating therapy, it is important to take time to educate caregivers (and older children) about regimen adherence and to anticipate and resolve any barriers that might diminish adherence. This is particularly true for children age ≥5 years given their lower risk of disease progression and the higher CD4 count threshold now recommended for initiating therapy.

If therapy is deferred, the health care provider should closely monitor the child's virologic, immunologic, and clinical status (see Laboratory Monitoring of Pediatric HIV Infection). Factors to consider in deciding when to initiate therapy in children in whom treatment was deferred include:

- Increasing HIV RNA levels (e.g., HIV RNA levels approaching 100,000 copies/mL);
- CD4 count or percentage values approaching the age-related threshold for consideration of therapy;
- Development of clinical symptoms; and
- The ability of caregiver and child to adhere to the prescribed regimen.

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